A THEORETICAL MECHANISTIC INVESTIGATION OF ASYMMETRIC AZIRIDINATION BY *N*-ARYL-*O*-ACYLHYDROXYLAMINES.

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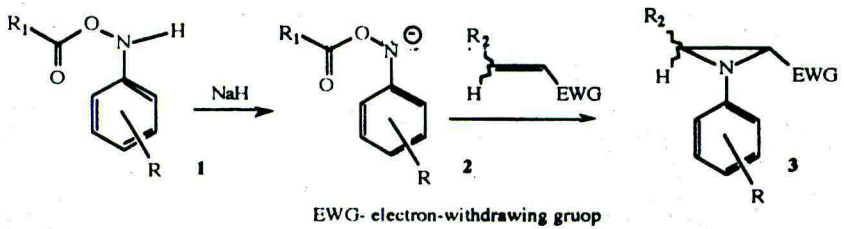
ABSTRACT

This paper reports a theoretical investigation of the most probable mechanism for the asymmetric aziridination of olefins by *N*-aryl-*O*-acylhydroxylamines. The transition states of two possible mechanisms (Scheme 2) were studied. The transition state for pathway 2 (oxaziridine as intermediate) has a lower energy of activation than the energy of the transition state for pathway 1. The anionic transition state of pathway 2 is more stable than the neutral transition state.

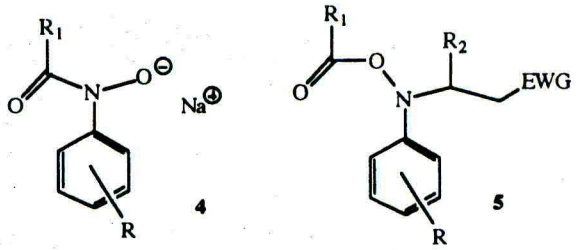
INTRODUCTION

In 1993 a new route for the synthesis of functionalised aziridines from the reaction of *N*-aryl-*O*-acylhydroxylamines with olefins in basic conditions was reported[1] (Scheme 1). The recently developed methods for the synthesis of *N*-aryl-*O*-acylhydroxylamines utilizing acylcyanides[2], 2-acylthiazolium salts[3] and 2-acylimidazolium salts[4], qualified this method as a potential choice for a route leading to aziridines. The anion **2** (R=H, R_1=Ph) generated from **1** (R=H, R_1=Ph) reacted with a Michael acceptor providing a new method for 2-substituted aziridines (**3**).



Scheme 1

The authors[1] observed complete stereospecifity for this reaction: only the *cis* aziridines were produced from the corresponding *cis* olefin. Also sodium hydroxamate (**4**), generated *in situ* from the corresponding hydroxamic acid, in the presence of the electrophilic phenyl vinyl sulfoxide, yielded the corresponding aziridine.

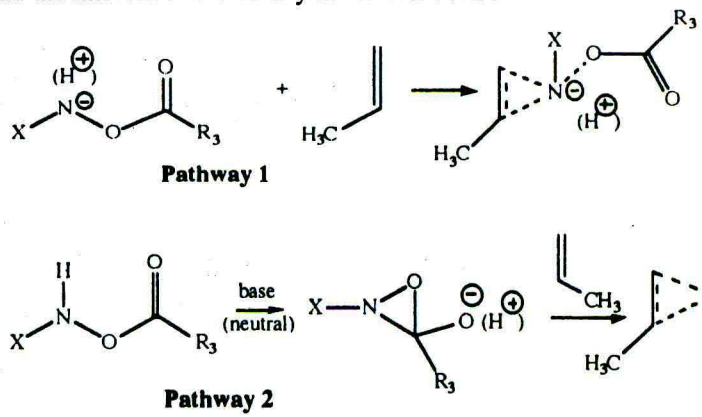


4 **5**

The incapacity of this aziridinating agent to produce the corresponding aziridines with cyclohexene, styrene or dihydropyran, shows its nucleophilic character, but not its nitrenic nature. Relevant to the study of this reaction are the following observations[1]:

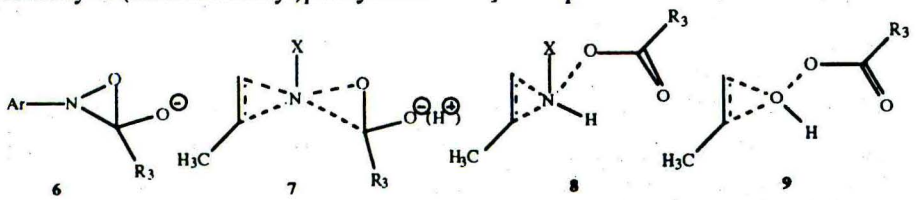
a) Species **1** reacts only with electron deficient alkenes in the presence of base to produce aziridines.
b) The Michael adduct (**5**) does not yield aziridine on treatment with bases, showing that it is not a precursor of the aziridine.
c) No aziridination occurs with *N*-acyloxyamine in the absence of base.
d) Slow addition of **1** to an excess of methyl acrylate and NaH, causes a significant increase in the yield of the aziridine. This could be explained by isomerisation of the hydroxamate ion *via* the isomeric oxaziridine to the *N*-acyloxyaniline anion, followed by a concerted attack on the electron-deficient olefin.
e) If R_1 is a chiral auxiliary, asymmetric aziridination can be detected[5].

This work is a contribution to the clarification of the rôle of hydroxamics acids and *N*-aryl-*O*-acylhydroxylamines as aziridinating agents of alkenes. The objective of this work is to determine which mechanistic pathway (pathway **1** or pathway **2**) is energetically more favorable (Scheme 2), the influence of substituents and the influence of chirality in the transition states.



Scheme 2

We report the results of *semi*-empirical SCF-MO calculations which indicate that a species such as **6** can act as the active nucleophilic aziridinating reagent, *via* a transition state such as **7** exhibiting an oxy-anion effect[6], as an alternative to the more classical transition states **8** (similar to those of epoxidation **9**[7,8]) and which may rationalise the above experimental observations. Diastereomeric energy differences for a chiral auxiliary (Q1 - Scheme 2) based on the *R* form of Mosher's acid [α-methoxy-α-(trifluoromethyl)phenylacetic acid] are reported.



EXPERIMENTAL

The optimization of transition states was carried in a Macintosh IIx with CAChe 3.0 installed. The chemical species were built in EDITOR 3.0 and the geometry optimization was done in MOPAC 94. The optimization of chemical species was done in the gas phase. The parametric method utilized in the simulation was the PM3.

RESULTS AND DISCUSSION

Table I - Activation energy and heat of formation (in parentesis) for the diferent neutral transition states (ts_a and ts_{aa}) of pathway 1 (Scheme 2).

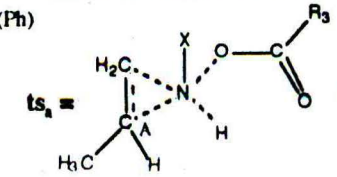
Entry	R_3	X	Configuration of carbon A: *R*		Configuration of carbon A: *S*	
			ts_a	ts_{aa}	ts_a	ts_{aa}
1	Q_1	H	32.75 (-69.63)	32.55 (-69.64)	32.65 (-69.73)	32.81 (-69.56)
2	H	Q_1	49.00 (-60.85)	50.81 (-58.67)	50.55 (-58.94)	48.74 (-60.75)

Notes:

Heat of formation and activation energy in Kcal.mol^{-1}.

Q_1 = *R*-CF(OH)(Ph)

ts_a =



ts_{aa} =

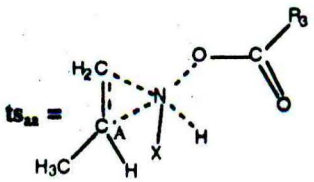


Table II - Activation energy and heat of formation (in parentesis) for the diferent anionic transition states (ts_b and ts_{ba}) of pathway 1 (Scheme 2).

Entry	R_3	X	Configuration of carbon A: *R*		Configuration of carbon A: *S*	
			ts_b	ts_{ba}	ts_b	ts_{ba}
1	Q_1	H	23.23 (-97.62)	20.00 (-100.00)	23.58 (-97.27)	19.63 (-100.38)
2	H	Q_1	31.78 (-109.17)	26.50 (-114.45)	32.14 (-108.81)	26.29 (-114.66)

Notes:

Heat of formation and activation energy in Kcal.mol^{-1}.

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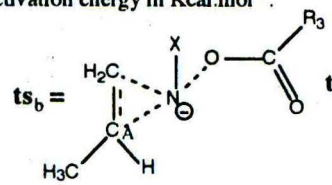
ts_b =



ts_{ba} =

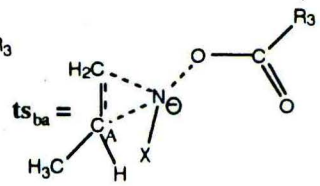


Table III - Activation energy and heat of formation (in parentesis) for the diferent neutral transition states (ts_c and ts_{ca}) of pathway 2 (Scheme 2).

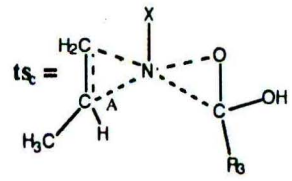
Entry	R_3	X	Configuration of carbon A: *R*		Configuration of carbon A: *S*	
			ts_c	ts_{ca}	ts_c	ts_{ca}
1	Q_1	H	23.11 (-57.31)	24.10 (-56.50)	21.80 (-58.62)	22.91 (-57.69)
2	H	Q_1	27.51 (-57.08)	28.78 (-57.34)	27.03 (-57.55)	29.34 (-56.78)

Notes:

Heat of formation and activation energy in Kcal.mol^{-1}.

Q_1=*R*-CF(OH)(Ph)

ts_c =



ts_{ca} =

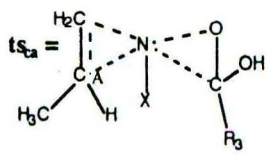


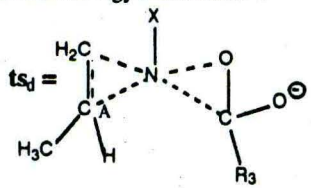
Table IV - Activation energy and heat of formation (in parentesis) for the diferent anionic transition states (ts_d and ts_{da}) of pathway 2 (Scheme 2).

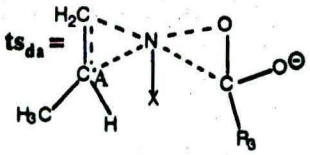
Entry	R_3	X	Configuration of carbon A: *R*		Configuration of carbon A: *S*	
			ts_d	ts_{da}	ts_d	ts_{da}
1	Q_1	H	8.66 (-116.26)	12.34 (-110.84)	8.72 (-116.19)	12.76
2	H	Q_1	20.47 (-121.78)	22.61 (-119.64)	21.39 (-120.86)	23.42 (-118.84)

Notes:

Heat of formation and activation energy in Kcal.mol^{-1}.

Q_1 = *R*-CF(OH)(Ph)

ts_d = 

ts_{da} = 

The results show that pathway 2, involving an oxaziridine - like transition state, is globally more favoured than pathway 1 (cf. tables I *versus* III and tables II *versus* IV). It is also apparent that the anionic transition state is more stable than the corresponding neutral one (cf. tables I *versus* II and tables III *versus* IV). This result is consistent with a reaction where the aziridinating species attacks nucleophilically the olefin.

For further information, see the following uniform resource locator (URL) for the world-wide-web; http://www.ch.ic.ac.uk/talks/aziridination.html

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COMBINED QUANTUMCHEMICAL AND MM-APPROACH TO THE ENDO/EXO-SELECTIVITY OF DIELS-ALDER REACTIONS IN POLAR MEDIA

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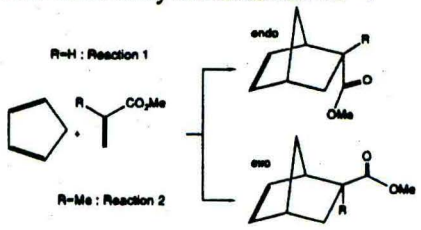
ABSTRACT

The endo/exo selectivity of the Diels-Alder reaction in polar solvents is studied with semi-empirical methods using the SCRF approach [9] and a combination of quantumchemical and molecular mechanics (QC/MM) to regard the effect of the solvent. By calculating the stabilization energies of different transition state structures in water, only the results for the QC/MM method are in good agreement with the experimentally observed selectivities[20]. Thus this method[15] proves to be a promising approach to study such complicated solute/solvent systems.

INTRODUCTION

Nevertheless, the strong dependence of the selectivity on the polarity of the solvent calls for a theoretical model that includes the effect of the solvent. This dependence was already studied in 1962 by Berson et al. [1]. Only recently, we found high exo-selectivities in the reaction of Cp with chiral capto-dative substituted olefins derived from lactic and malic acid [2].

The mechanism of the Diels-Alder reaction has been subject of numerous publications focusing on the explanation of the experimentally observed endo-selectivity [3]. Yet, simple arguments (e.g. secondary orbital overlap [4]) do not give a conclusive explanation. Therefore the determination of the transition state (TS) geometry by quantumchemical methods is necessary. While the semiempirical MNDO method gives an unrealistic transition state (TS) [5] AM1 [6] is well suited for modeling this reaction [7] comparable to results of *ab initio* studies [8] On the other hand, AM1 reveals a strong preference for the formation of the exo-product Lately, Jorgensen et al. were able to reproduce the experimental selectivity in non-polar solvents in an *ab initio* study of the isolated TS [8].



scheme 1

We report here the results for the simple reactions studied by Berson et al. [1] with different solvation models with emphasis on a combination of quantumchemical methods and molecular mechanics (QC/MM). This model accounts for specific interactions between solute and solvent.

THE SOLVENT MODELS

Like Cativiela et al. [9], we used the SCRF model as implemented in the GEOMOS program [10] to study the reactions 1 and 2 in water. In both cases, the TSs leading to the exo adduct were calculated to be thermodynamically more stable which is in contrast to the experiment